IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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Inventors:	Nashimoto et al.
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Examiner:	Orwig, Kevin S.
Customer No.:	26259
Group Art Unit:	1611
Confirmation No.:	5791
Title:	Anti-Inflammatory Analgesic Preparation

Declaration by TSURUDA, Kiyomi

I, TSURUDA, Kiyomi hereby declare:

1. I am a co-inventor of the above-referenced patent application and familiar with its teachings.

2. I am also a co-inventor of WO 01/68061 and U.S. Patent 6,924,410 and Published U.S. Application No. 2003/0109819 and thus am familiar with their teachings as well.

3. We performed mouse ear irradiation experiments to compare the effects of compositions containing ketoprofen and different UV blockers on swelling. Ear swelling is one of the side effects caused by decomposition products (i.e. radicals) of nonsteroidal antiinflammatory drugs (NSAIDs). Balb/c mice (female, 9-11 weeks of age) were used in these experiments. Ethanol solutions containing 2% of the NSAID ketoprofen and either 3% 4-tert-butyl-4'-

methoxydibenzoylmethane (BM-DBM), 3% Mexoryl® XL (a lipophillic benzotriazole derivative obtained from Nihon L'Oreal, Inc., IUPAC name 2-(2H-benzotriazol-2-yl)-4-methyl-6-[2-methyl-3-[1,3,3,3-tetramethyl-1-(trimethylsilyl)oxy]disiloxanyl]propyl] phenol), or no UV blocker (referred to as controls) were applied to the ear of mice, followed by irradiation of 40 J/cm^2 of UVA. Thicknesses of the ears after 24 hours irradiation were then measured and their increases compared. Results are shown in Figure 1 attached hereto.

4. As shown by Figure 1, both solutions containing UV blockers suppressed the increase in ear thickness indicative of swelling as compared to solutions containing no UV blocker (controls). However, 3% BM-DBM reduced ear swelling by about 55% compared to the controls while 3% Mexoryl® XL reduced ear swelling by only about 20% compared to the controls. Accordingly, BM-DBM was 2.75 times more effective at preventing photodecomposition of the NSAID ketoprofen to its radical form than the benzotriazole derivative Mexoryl® XL and is expected to be a significantly better stabilizer of the rubber system macromolecule than the benzotriazole derivative Mexoryl® XL.

5. I am also providing with this Declaration absorption curves from two publicly available documents relating to the UV blockers Mexoryl® XL and avobenzone (also known as BM-DBM) and 2-(2-hydroxy-5-methylphenyl)benzotriazole. Absorption curve A depicting Mexoryl® XL and avobenzone (BM-DBM) is an English language translation of Figure 10A from a reference by Forestier et al. Fragr. J. 2004 32(4):59-64). A copy of the English language Abstract of this reference is

also provided herewith. Absorption curve B is an English language translation of Figure 4 from the patent publication JP H10-59987 A. According to these curves, Mexoryl® XL and 2-(2-hydroxy-5-methylphenyl)benzotriazole have similar absorption curves, while that of avobenzone (BM-DBM) is different. The best effective absorption wavelength of avobenzone is longer than that of the two benzotriazole derivatives. As one skilled in this art, I would expect Mexoryl® XL and 2-(2-hydroxy-5-methylphenyl)benzotriazole to function similarly in transdermal patches given their similar absorption curves. I would not expect avobenzone (BM-DBM) to necessarily function in the same manner as Mexoryl® XL and 2-(2-hydroxy-5-methylphenyl)benzotriazole in transdermal patches based upon their differing absorption curves and it was completely unexpected that BM-DBM would function so much more effectively, specifically, 2.75 times more effectively, than the benzotriazole derivative Mexoryl® XL.

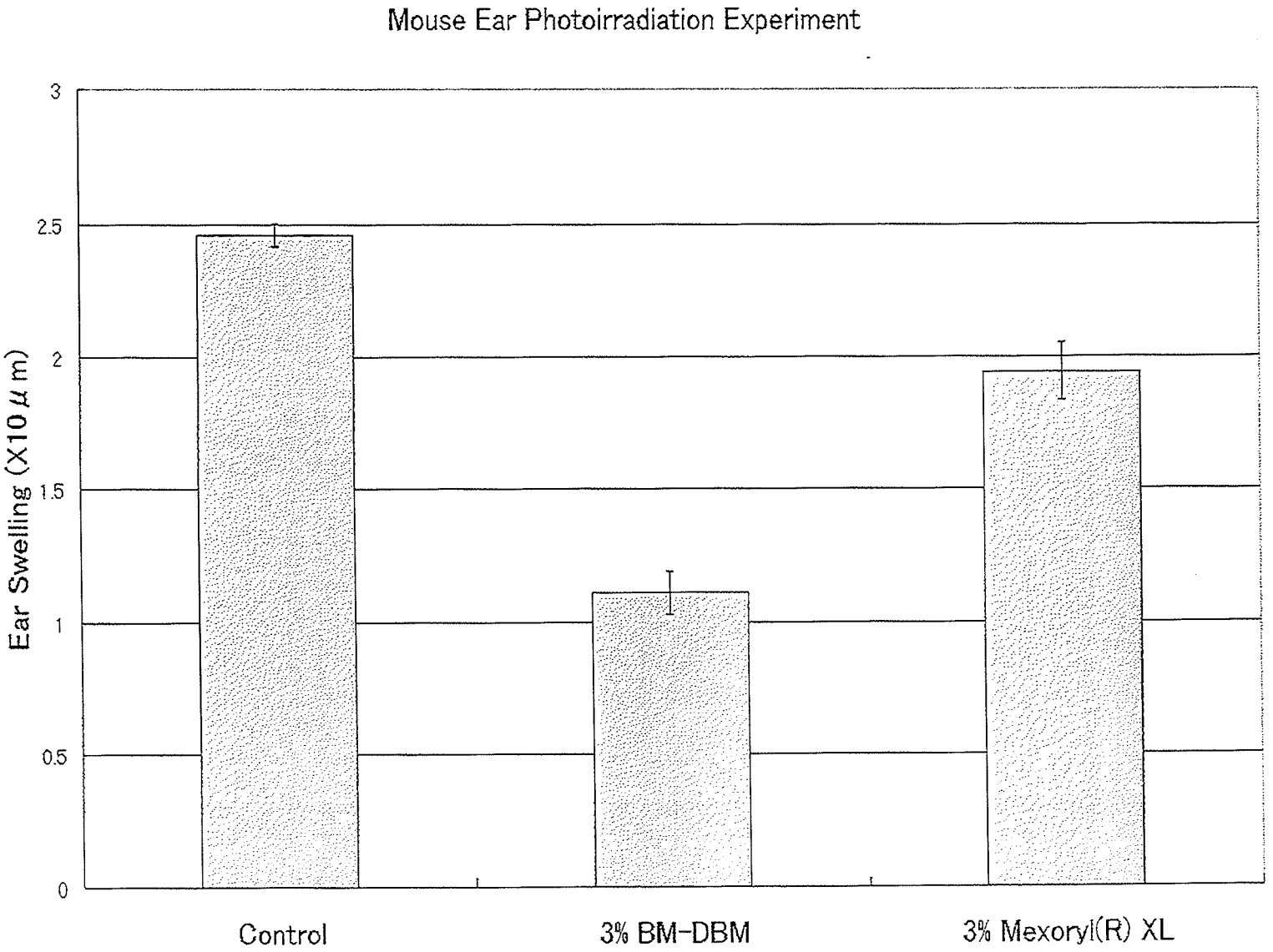
I hereby declare that all statements herein of my own knowledge are true and that all statements made on information or belief are believed to be true; and further that these statements were made with the knowledge that willful statements and the like so made are punishable by fine or by imprisonment, or both, under §1001 of Title 18 of the United States code, and that such willful statements may jeopardize the validity of the application, any patent issuing there upon, or any patent to which this verified statement is directed.

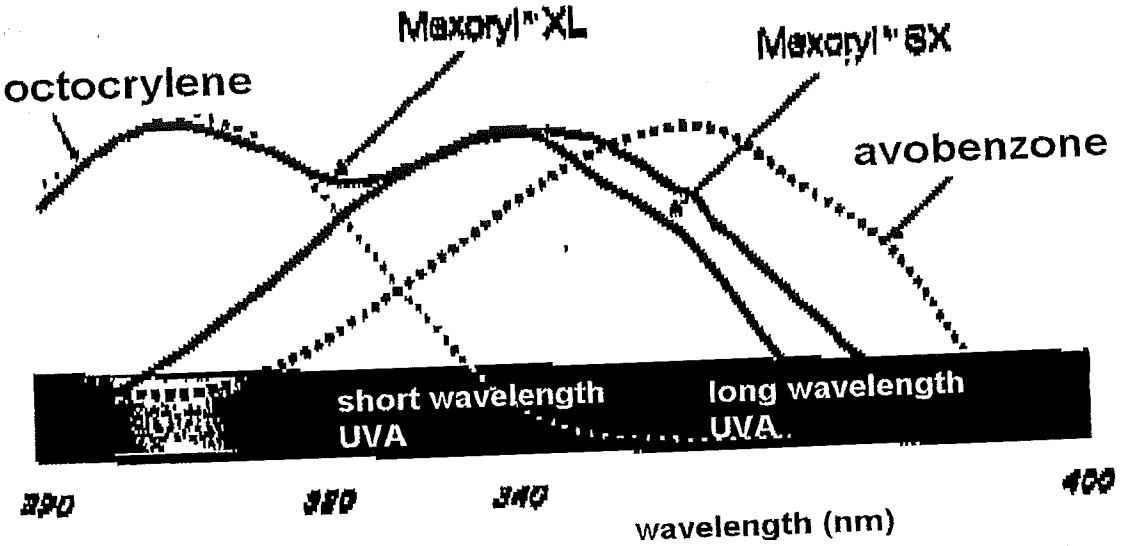
Kiyomi Tsuruda

TSURUDA, Kiyomi

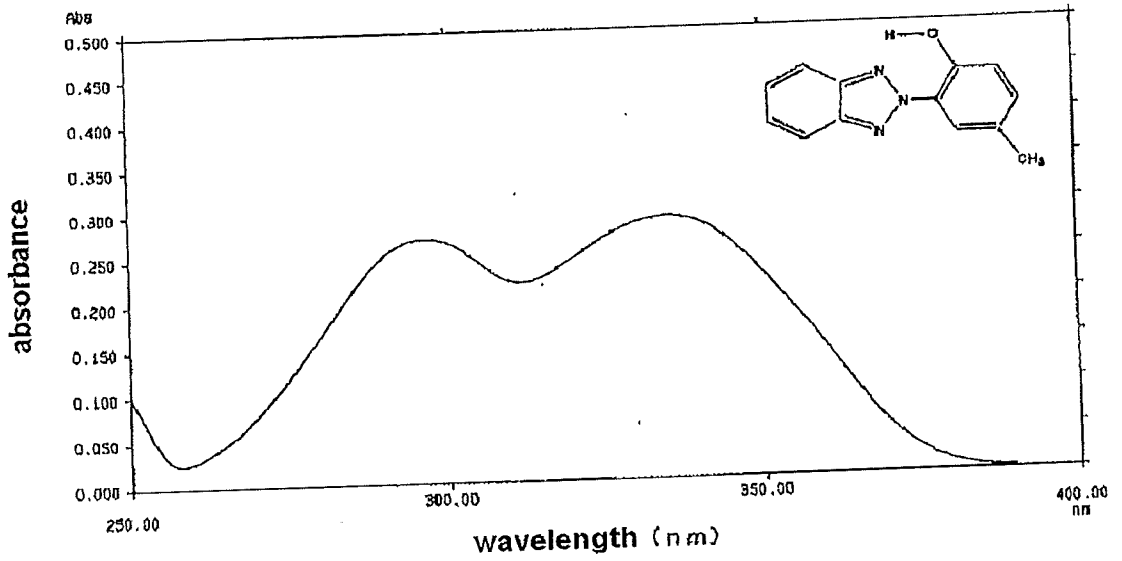
Date: Sep. 30, 2010

FIGURE 1


Mouse Ear Photoirradiation Experiment
Ear Swelling (X10 μ m)
3
2.5
2
1.5
1
0.5
0
Control
3% BM-DBM
3% Mexoryl(R) XL



ABSORPTION CURVE A



ABSORPTION CURVE B

紫外線防御剤Mexoryl® XLの開発と製品への応用

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Abstract : Mexoryl® XL (a hydroxyphenyl benzotriazole derivative) is a new UV protective agent developed by L'Oréal. The molecule is safe and stable, and absorbs UVB as well as UVA. This UV absorber exerts UV protection by converting the absorbed light energy into thermal one via its keto-enol tautomerism. Mexoryl® XL increases its UV protection efficiency (PFA and SPF) when it is used with Mexoryl® SX, another UV protective agent (UVA specific absorber). A photoprotective formulation with UV protective agents of different absorbance specificity (Mexoryl® XL, Mexoryl® SX, octocrylene and avobenzone) was found to be effective for preventing photo-induced skin problems, such as polymorphous light eruption and photosensitive lupus erythmatosus. Mexoryl® XL was approved by the Ministry of Health, Labor and Welfare in December 2002 and the first product "Anthélios XL" has been launched on the Japanese market since February 2003.

Key words : UV protection, sunscreen, UVA absorber, UVB absorber, Mexoryl® XL

1．はじめに

地表に到達する紫外線は波長の短いUVB（280～320nm）および波長の長いUVA（320～400nm）の2種類に大別される。UVBはエネルギーが高く，短期的には紅斑もしくは日光皮膚炎（サンバーン）等の原因であり，長期的には皮膚ガンの原因にもなりうる。一方，UVAはエネルギーは低いが皮膚の奥深く浸透し，真皮にまで達する。近年さまざまな研究により，UVA，特に波長の短いUVAが光老化の過程に深く関与していることが分ってきた[1]。また，免疫抑制[2]の誘発や，UVBとは異なる様式でのDNA損傷[3]も報告されている。したがって，全スペクトル領域にわたり紫外線から生体を防御することが，皮膚外観の面だけではなく，健康維持のためにも必要である。ロレアル社では1980年以降，光化学に関するさまざまな研究を行っており，その成果は当社の製

"Mexoryl® XL : A new UV protective agent."

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